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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,258	07/21/2005	Min-Ho Shong	20050-00003	2722

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EXAMINER	
WORLEY, CATHY KINGDON	
ART UNIT	PAPER NUMBER
1638	

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12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,258	SHONG ET AL.	
	Examiner	Art Unit	
	CATHY K. WORLEY	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-13 and 15-22* is/are pending in the application.

4a) Of the above claim(s) *6,11-13,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7-10, and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on Oct. 6, 2008, has been entered.

2. Claims 5 and 14 have been cancelled.

Claims 15-22 have been newly added.

Claims 1-4, 6-13, and 15-22 are pending.

New claims 21 and 22 are directed to an invention that was not elected in the response filed on May 8, 2007, therefore these claims are withdrawn from consideration.

Claims 6, 11-13, 21, and 22 are withdrawn.

3. Claims 1-4, 7-10, and 15-20 are examined in the present office action.

Rejections that are Withdrawn

4. The rejection of claims 1-4 and 7-10 under 35 USC 103 is withdrawn in light of the Applicant's amendments to the claims.

Claim Objections

5. Claims 1, 7, 15, and 16 are objected to because of the following informalities: they continue to recite hTSHR-ECD which was not elected in the response filed on May 8, 2007, in which the Applicant elected to prosecute the invention of Group I and not the invention of Group II (see restriction requirement mailed on April 9, 2007). The Applicant is advised to delete all recitations of hTSHR-ECD.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 7-10, and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitelam (J. Sci. Food Agric. (1995) Vol. 68, pp. 1-9) in view of Stiens et al (Biotechnol. Prog. (2000) Vol. 16, pp. 703-709) and further in view of Chrispeels et al (Trans. Plants: A production Sys. For Indust. And Pharm. Proteins (1996); ed. Owens and Pen; John Wiley & Sons, Ltd.; pp. 99-113). The Applicant's arguments in the response filed on Oct. 6, 2008, were fully considered but were not found to be persuasive.

The claims are drawn to a method of producing transformed plants expressing zoonosis free human thyroid stimulating hormone receptor (hTSHR), including wherein said hTSHR binds a serum auto-antibody from a patient with autoimmune thyroid disease, including hyperthyroidism and Grave's disease.

Whitelam teaches the production of recombinant proteins in plants, including the use of an *Agrobacterium tumefaciens* binary vector system to transform tobacco plants, which are *Nicotiana tabacum* (see page 3, left column). Whitelam teaches the use of the CaMV 35S promoter which functions in plants (see page 3, left column). Whitelam teaches purification of a recombinant protein from a transgenic plant (see page 2, right column). Whitelam teaches that mRNA from a transgene was produced in the plant (see third paragraph on page 6) which indicates that the construct comprised a functional polyadenylation signal. Whitelam teaches the selection of a stable transgenic line (see second paragraph on page 4), and the steps of selecting transformed plant cells and regenerating a plant from said cells in order to generate a stable transgenic line are necessary steps that are well-known in the art and are required in order to generate a stable transgenic plant, therefore they are in intrinsic part of the method taught by Whitelam.

Whitelam does not teach recombinant hTSHR or binding of hTSHR to antibodies. Whitelam is silent with regard to zoonosis (which are infective agents, such as viruses or prions, that are transmitted too humans by vectors).

Stiens et al teach recombinant hTSHR produced in human leukemia cells (see last paragraph on page 704). Stiens et al teach that Grave's disease is a form of hyperthyroidism which is an autoimmune disorder of the thyroid, where the presence of autoantibodies to TSHR causes thyrotoxicosis (see left column on page 703) and they teach that they produced quality TSHR that bound to antibody in antibody-coated tubes (see page 705), which demonstrates that it was soluble. Therefore, recombinant hTSHR has the intrinsic property of being soluble and binding to autoantibodies in Grave's disease patients.

Chrispeels et al teach production of recombinant glycoproteins in plants, and specifically cite the absence of viruses and prions as one reason that plants are preferable over purifying proteins from blood (see paragraph bridgine pages 99-100).

At the time the invention was made, it would have been obvious and within the scope of one of ordinary skill in the art to utilize the methods taught by Whitelam to produce the hTSHR taught by Stiens et al. One would have been motivated to do so because Stiens et al teach that recombinant hTSHR has commercial value for use in diagnostic tests (see Stiens, second paragraph, left column, page 703). One would have been motivated to utilize a plant expression system because Chrispeels et al teach production of recombinant glycoproteins in plants is safe because of the absence of viruses and prions that can be in proteins from blood (see paragraph bridgine pages 99-100). Given the success of Stiens et al

in producing recombinant hTSHR and given the successes of producing other recombinant therapeutic proteins in transgenic plants taught by Whitelam, one of ordinary skill in the art would expect to succeed in expressing hTSHR in transgenic plants.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (In re Opprecht 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); In re Bode 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In order to fully appreciate the obviousness of the instant claims, one must consider that state of the art at the time of filing (July of 2002). By 2002, it was common practice to produce proteins in plants; as evidenced by the following reviews: Giddings, G. "Transgenic Plants as Protein Factories" (Current Opinion in Biotech. (2001) Vol. 12, pp. 450-454); Rishi et al. "Molecular Farming in Plants: A Current Perspective" (J. Plant Biochem. & Biotech. (2001) Vol. 10, pp. 1-12); Hansen, E. "Production of recombinant antigens in plants for animal and human

immunization – a review" (Brazilian J. of Genetics (1997) Vol 20, pp. 703-711); Lemaux et al. "The Production of Proteins in Plant Seeds" (WO 99/16890; published on April 8, 1999); and Goodman et al "Mammalian Peptide Expression in Plant Cells" (US Patent No. 4,956,282; issued on Sept. 11, 1990). The Examiner has relied on Whitelam and Chrispeels to teach the precise limitations in the instant claims; however, it is important to understand that the state of the art at the time of filing was such that production of recombinant proteins in plants was routine.

The Applicant argues that the references do not teach hTSHR-ECD (see last paragraph on pages 5-9 of the response). This is not persuasive, because this is not the elected invention. None of the arguments directed to hTSHR-ECD are pertinent to the elected invention, which is hTSHR.

The Applicant argues that Whitelam does not teach a soluble hTSHR or an hTSHR that binds an autoantibody from a human subject (see last paragraph on page 5 of the response). The Applicant argues that Whitelam does not report expression of any mammalian receptor protein in a plant expression system or a protein with a transmembrane domain (see page 6 of the response). This is not persuasive, however, because the rejection was based on the combination of references, it was not based on Whitelam alone. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of

references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The Applicant argues that there are unexpected results in producing hTSHR as a soluble polypeptide (see bottom of page 6). This is not persuasive, however, because the hTSHR produced by Stiens was soluble as evidenced by its use in a binding assay (see page 705).

The Applicant argues that Whitelam teaches that expression of fully native mammalian cell proteins containing signal sequences leads to partially processed proteins and that challenges exist for plant based expression of mammalian cell proteins (see paragraph bridging pages 6-7 of the response). This is not persuasive, however, because the field of molecular farming was very well-developed by 2002, and tools and strategies for expression of properly processed proteins were well-known; as evidenced by Whitelam's teaching of the use of a PRS signal sequence (throughout the article) or the use of oleosin fusions (see page 2) or the use of viral capsid proteins for presentation of peptides (see right column on page 6). The teachings of Whitelam are just some of the strategies employed by 2002 for expression of mammalian proteins in plants.

The Applicant argues that one would not have a reasonable expectation of success in the expression in plants of hTSHR including its native signal sequence (see third paragraph on page 7 of the response). This is not persuasive, however, because the instant claims do not require the inclusion of the native signal

sequence. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the native signal sequence of hTSHR) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The Applicant argues that Stiens et al teach that expression of hTSHR is unpredictable and produced low levels of expression in CHO and COS cells; and therefore, one would not have had a reasonable expectation of success in producing hTSHR in plant cells (see paragraph bridging pages 7-8 of the response). This is not persuasive, however, because Stiens et al taught that they were successful in producing hTSHR and others were successful in producing it in CHO and COS cells, albeit at low levels. There is no limitation in the instant claims that any particular expression level must be achieved, therefore, even a low level of expression would satisfy the instant claims and would constitute a success.

The Applicant argues that Stiens et al teach the production of TSH-R localized to the cell surface of intact K562 cells (see second paragraph on page 8 of the response). The Examiner can not find where Stiens et al teach expression on the surface of the cells; and in fact, the Examiner's understanding of Stiens et al is that the perfusion method relies on secretion of the protein to the medium while the cells are immobilized. Therefore, this argument is not persuasive. If the Applicant

can point out where Stiens et al state that the expression is on the surface of the cells, then the Examiner will find a different reference teaching expression of soluble hTSHR.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHY K. WORLEY whose telephone number is (571)272-8784. The examiner is on a variable schedule but can normally be reached on M-F 10:00 - 4:00, with additional variable hours before 10:00 and after 4:00 with additional variable hours before 10:00 and after 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Cathy K. Worley/
Primary Examiner, Art Unit 1638